Women Have Lower Tonic Autonomic Support of Arterial Blood Pressure and Less Effective Baroreflex Buffering Than Men

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Background—Short-term and tonic regulation of arterial blood pressure (BP) differ in premenopausal women and men of similar age.1–4 The autonomic nervous system (ANS) plays a critical role in BP regulation. With regard to short-term BP regulation, baroreflexes are an important mechanism by which the central nervous system controls BP in response to acute challenges imposed by stress, vasoactive drugs, and other stimuli. The ability of baroreflexes to “buffer” acute changes in BP under such conditions (ie, baroreflex buffering [BRB]) is reduced in certain physiological9 and disease10 states associated with impaired short-term BP regulation and/or altered responsiveness to vasoactive medications. In light of previous reports of less effective short-term regulation of BP in women than in men,1,2,6,11–14 we also hypothesized that premenopausal women have lower BRB of BP than men of similar age.

Methods and Results—To test these hypotheses, we performed direct measurements of tonic ANS support of BP and BRB of BP in groups of healthy premenopausal women and age-matched men. We also measured resting sympathoadrenal activity and systemic α1-adrenergic vascular responsiveness, 2 key determinants of these expressions of ANS control of BP.7,9,10,15,16 to determine their potential mechanistic roles in any gender-related differences observed.

Key Words: baroreceptors ■ nervous system, autonomic ■ sex

Short-term and tonic regulation of arterial blood pressure (BP) differs between premenopausal women and men of similar age.1–4 The autonomic nervous system (ANS) plays a critical role in BP regulation. Surprisingly, however, little or no direct evidence exists regarding possible gender-related differences in ANS control of BP in humans. With respect to tonic BP control, premenopausal women have lower resting BP, particularly systolic BP (SBP), than men.2,5,6 The ANS provides tonic support for resting BP, and we recently established that basal sympathetic nervous system activity is a key physiological determinant of the amount of tonic BP support provided by the ANS.7 Because premenopausal women tend to have lower resting sympathetic activity than men,2–4,8 we hypothesized that women have lower tonic ANS support of BP than men.

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Methods

Subjects
Fifty-one young adults, 22 premenopausal women (aged 28±1 years) and 29 men (aged 27±1 years), were studied. Men and women were recruited from the community with flyers and newspaper advertisements. More than 80% of the subjects in each group were white. Subjects were normotensive (BP <140/90 mm Hg) nonsmokers who were not taking any medications. None of the women were using hormonal contraception. All subjects were considered to be healthy on the basis of medical history, physical examination, urinalysis, blood chemistries, and resting ECGs. The nature, benefits, and risks of the study were explained to the volunteers, and their written informed consent was obtained before the study. Data collection on all subjects was performed at the General Clinical Research Centers of the University of Colorado’s Health Sciences Center and Boulder campuses and Vanderbilt University Medical School. Procedures were approved by the institutional review boards of these institutions and were in accordance with their respective guidelines.

Autonomic-Cardiovascular Function

Subjects were studied during supine rest according to procedures previously described.7,9 In general, BP (mm Hg) was continuously monitored by a pressure transducer (radial or brachial artery catheter). Heart rate was measured via ECG. Plasma samples were analyzed for catecholamines17 concentrations. In a subgroup of 8 premenopausal women and 8 men (both groups aged 26±1 years), we measured plasma vasopressin18 concentrations before and during ganglionic blockade (GB).

ANS support of BP was determined as the reduction in BP from baseline during GB achieved by blockade of N2-cholinergic receptors via continuous intravenous infusion of trimethaphan (on average 6 to 7 mg/min).7 The trimethaphan dose was not based on body weight; instead, trimethaphan infusion began at 2 mg/min and was increased incrementally until complete GB was documented. This effective blocking dose was maintained throughout the experimental session. Complete cardiovascular-autonomic blockade was documented by an absence of change in heart rate (<5 bpm) in response to the acute increase in BP (≥15 mm Hg) produced by bolus administration of phenylephrine (25, 50, and/or 100 μg). BRB was measured in a subgroup of 14 women and 14 men (aged 26±1 and 27±1 years, respectively) as the potentiation of the SBP response to a standard 25-μg bolus dose of phenylephrine during GB compared with before GB.19,20 The increase in SBP in response to phenylephrine during GB was used to determine systemic α1-adrenergic vascular responsiveness.20 Cardiovagal baroreflex sensitivity (BRS) was determined at baseline (ie, before trimethaphan) in a subgroup of 12 women and 12 men (27±1 and 26±1 years, respectively) by administering incremental bolus doses of phenylephrine (25, 50 100, 200 μg) at 3-minute intervals and regressing R-R intervals against SBP.21,22

Data Analysis

Statistical analyses were performed with the SPSS (version 11.0) statistical package. Gender comparisons were made with t tests for independent samples. Responses to trimethaphan were analyzed with repeated-measures ANOVA with condition (baseline versus GB) as the within-subject factor and gender as the between-subject factor. The gender-by-condition interaction was of particular interest. ANCOVA was used to control for baseline differences in SBP between the 2 groups. Curve estimation analysis was used to fit the curvilinear relation between BRB and the increase in SBP in response to phenylephrine at baseline. Visual inspection of the fit of the model, examination of the R² and associated probability values, and examination of the distribution, normality, and autocorrelation of the residuals were the criteria used to choose the most appropriate model. Alpha was set at 0.05. All data are reported as mean±SE.

Results

The Table shows selected characteristics of the 2 subject groups. Weight, body mass index, SBP, plasma norepinephrine and epinephrine concentrations, and cardiovagal BRS (16±1 versus 24±3 ms/mm Hg) were lower in the women compared with the men (P<0.05), whereas mean and diastolic BP and heart rate were not different in the 2 groups (P>0.05).

Tonic ANS Support of BP

SBP and mean and diastolic BP decreased in both groups in response to GB (all P<0.001 versus baseline; Figure 1); however, the reductions were ~50% to 65% smaller in the women (P<0.001). A smaller reduction in BP during GB was related to lower baseline plasma catecholamine concentrations (r=-0.31 to -0.41, P<0.05 to 0.01). A smaller reduction in SBP during GB also was related to a lower baseline SBP (r=-0.45, P=0.001); however, the group differences were still highly significant (P=0.001) after covarying for baseline SBP.

Heart rate increased (P<0.0001 versus baseline) similarly (25.2 versus 24±2 bpm, P=0.8) in the 2 groups in response to GB. Plasma vasopressin concentrations increased (P<0.05) in response to GB in both groups, but the increases were smaller in the women (0.5±0.1 ng/L at baseline to 8.0±4.3 ng/L during GB versus 0.7±0.1 to 54.2±23.7 ng/L, P<0.05).

Baroreflex Buffering

At baseline (before GB), the increase in SBP in response to phenylephrine was 105% greater in the women (7.6±0.9 versus 3.7±0.5 mm Hg, P=0.001; Figure 2), whereas the increases in SBP in response to phenylephrine during GB were not significantly different in the 2 groups (21.5±2 mm Hg in women versus 18.6±2 mm Hg in men, P=0.3; Figure 2). As a result, potentiation of the SBP response to phenylephrine during GB (ie, BRB) was 47% smaller in the women (3.3±0.5-fold versus 6.3±0.9-fold, P<0.001; Figure 2). BRB was strongly inversely and curvilinearly related to the increase in SBP in response to phenylephrine at baseline (R²=0.71, P<0.0001; BRB=14ΔSBP in response to phenylephrine bolus)−0.8; Figure 3). BRB was not related to baseline SBP, BRS, or any other subject characteristic (all P>0.05).
Discussion

The major novel findings of this study include the following. First, healthy premenopausal women have lower tonic ANS support of BP than healthy men of similar age. The lower tonic ANS support of BP in women is related in part to their lower basal sympathoadrenal system activity. Second, premenopausal women have less effective BRB of BP than young men. Third, systemic α₁-adrenergic vascular responsiveness is not different in healthy premenopausal adult women and men of the same age. These findings provide the first direct experimental evidence in humans that these fundamental properties of short-term and tonic ANS control of BP differ between women and men.

Tonic ANS Support of BP

We recently established that basal sympathetic nervous system activity, as reflected in part by plasma norepinephrine concentrations, and systemic α₁-adrenergic vascular responsiveness are the 2 primary physiological correlates of tonic ANS support of BP in healthy men. In the present study, the reductions in BP during GB were significantly related to

Figure 1. Responses to GB in young men and women. MAP indicates mean arterial pressure; DBP, diastolic BP. Values are mean ± SE.

Figure 2. Top, increase in SBP (ΔSBP) in response to 25-μg bolus of phenylephrine before (baseline) and during GB in young men and women. Bottom, BRB in young men and women as determined by potentiation of SBP responses to phenylephrine bolus during GB. Values are mean ± SE.

Figure 3. Relation between BRB of BP and increase in SBP in response to 25-μg bolus of phenylephrine (Phe) at baseline (ie, before GB). Power function: BRB = 14(ΔSBP in response to phenylephrine bolus)^0.8 provided best fit for data.
basal plasma catecholamine concentrations, which supports the idea that the lower resting sympathoadrenal activity in the women contributed to their lower tonic ANS support of BP. The underlying mechanisms are uncertain, but presumably smaller tonic sympathoadrenal stimulation of cardiac output and/or systemic vascular resistance is involved. In contrast, the increases in SBP in response to phenylephrine during GB were not different in men and women in the present study, which indicates that differences in systemic \(\alpha_1\)-adrenergic vascular responsiveness did not contribute to gender-related differences in tonic ANS support of BP. The present results represent the first direct measurements of systemic \(\alpha_1\)-adrenergic vascular responsiveness in men and women and correct previous findings of gender-related differences in responsiveness based on BP responses to systemic infusions of \(\alpha_1\)-adrenergic agonists with intact baroreflexes.

We have shown that circulating levels of vasopressin increase in response to the decrease in BP produced by GB. The vasoconstrictor effects of vasopressin can counteract the reductions in BP during GB and thus lead to an underestimation of tonic ANS support of BP. In the present study, however, the vasopressin response to GB-mediated hypotension was modest in the women but much greater in the men. Thus, if anything, this difference in the vasopressin counterregulatory responses to GB would have caused an underestimation of the true gender-related differences in tonic ANS support of BP in the present study.

**Baroreflex Buffering**

Because the magnitude of the BP response to vasoactive drugs is the net effect of vascular sensitivity to the drug (\(+\)) and the counterregulatory actions of the baroreflexes (\(\rightarrow\)), the potentiation of the BP response to phenylephrine during GB (absence of baroreflexes) compared with baseline (intact baroreflexes) provides a measure of the in vivo capacity of the baroreflexes to buffer acute changes in BP. Recently, we have used this model to examine BRB in patients with ANS-cardiovascular disorders, as well as healthy young and older men. The results of these studies indicate that differences in BRB among groups or individuals are not consistently related to resting BP, heart rate, or cardiovagal BRS, nor was BRB by the present phenylephrine bolus technique related to basal plasma catecholamine concentrations. Rather, of relevance to the present study, BRB was positively related to systemic \(\alpha_1\)-adrenergic vascular responsiveness among healthy men. The physiological basis for this latter relation is that the neurovascular coupling between sympathetic nerve discharge, norepinephrine release, and the responsiveness of the vascular smooth muscle to the consequent \(\alpha_1\)-adrenergic stimulation is the final step in the sympathetic-vasoconstrictor arm of the baroreflexes.

In the present study, BRB was not significantly related to baseline cardiovascular function, plasma catecholamine concentrations, or any other subject characteristic, which suggests that neither differences in resting BP, tonic sympathoadrenal activity, nor any other baseline factor were mechanistically involved in the gender-related differences in BRB. Moreover, systemic \(\alpha_1\)-adrenergic vascular responsiveness was not different in the men and women and did not correlate with BRB in the pooled group of subjects. As reported previously, baseline cardiovagal BRS was lower in the women. In agreement with our previous observations, however, cardiovagal BRS was not consistently related to BRB, which reinforces the important point that the 2 measures represent different properties of the baroreflexes. The differences in BRB among women and men in the present study, therefore, are mediated by 1 or more currently undetermined differences in the afferent, central regulatory, or ANS efferent elements of the baroreflexes.

The present investigation, we found that the SBP response to phenylephrine at baseline was greater in women than in men, in agreement with an earlier report. We previously demonstrated that BRB is strongly and inversely related to this pressor response to phenylephrine in healthy men and patients with ANS-cardiovascular disorders. In the present study, we found a similarly strong, inverse curvilinear relation among the pooled male and female subjects (Figure 3). Given that systemic \(\alpha_1\)-adrenergic vascular responsiveness was not different in the men and women, this relation suggests that the greater SBP response to phenylephrine at baseline in the women reflects a reduced capacity for BRB of BP. Indeed, as emphasized previously, the consistency of this relation indicates that the baseline SBP response to a standard 25-\(\mu\)g bolus of phenylephrine can be used to identify impaired BRB among both healthy adults and patients with chronic diseases that adversely affect baroreflex function. The flat portion of the curve indicates that individuals demonstrating SBP responses to phenylephrine of more than \(+5\) mm Hg at baseline (ie, with intact baroreflexes) have similarly low BRB capacity.

**Study Limitations**

In the present investigation, we only used a vasoactive drug that produced increases in BP (ie, phenylephrine) to determine BRB, rather than in combination with a drug that produced reductions in BP (eg, nitroprusside). This was because systemic administration of vasodilators such as nitroprusside during GB in normotensive adults can cause BP to fall to levels associated with inappropriately high risks, particularly for healthy volunteers. However, Jordan and colleagues have demonstrated that the same group differences in BRB are revealed when phenylephrine or nitroprusside is used. In addition, the trimethaphan and phenylephrine doses used in the present study were not based on body weight. Given the differences in body weight in men and women in the present study, one might question whether this factor influenced our results. However, although the amount of trimethaphan administered was not weight-based, the dose was adjusted until complete GB was produced and confirmed. Moreover, body weight did not influence the BP responses to the standard bolus of phenylephrine administered, because the effect of gender was unaffected after statistically covarying for body weight. Finally, measurements in the women were not obtained during a standardized phase of the menstrual cycle. Measurement of some ANS-cardiovascular functions differ between phases of the menstrual cycle. It is possible that measures of ANS function in the present study may have been different in the women in other phases of their cycle.
menstrual cycle; however, the lack of standardization in the present study would have introduced more variability into the data. We were able to demonstrate highly significant group differences in the key outcomes despite this factor.

**Clinical Implications**

Premenopausal women typically have lower resting BP, particularly SBP, than young men,1-3,6 but the underlying mechanisms are poorly understood. The results of the present study indicate that less tonic ANS support may be 1 mechanism that contributes to the lower resting BP in young women. The fact that the lower ANS support of SBP in the women was related to their lower resting SBP is consistent with this possibility. Moreover, women often demonstrate less effective BP regulation than men during acute challenges (eg, orthostatic stress) and in response to vasoactive drugs.1,2,4,6,11-14 The responsible mechanisms have not been identified, but the results of the present study indicate that a reduced ability for BRB of acute changes in BP may play a central role in the less effective short-term BP control observed in women.

We also wish to emphasize the magnitude of the gender-related differences in tonic ANS support of BP and BRB of BP observed in the present study. The gender-group differences were generally as great or greater than those observed between young and older healthy men7,9 and between healthy men.10,16 Thus, consistent with previous reports of gender-related differences in other ANS-cardiovascular functions,1-4,8,23-25 the present findings indicate that subject gender is a major source of interindividual variability in tonic ANS support of BP and BRB of BP in healthy adult humans.

**Conclusions**

Premenopausal women have lower tonic sympathoadrenergic activity-related ANS support of BP and less effective BRB of BP than men of similar ages. These findings may provide novel insight into the physiological mechanisms underlying gender-related differences in short-term and tonic regulation of BP in humans.

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**References**

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